formulation developed by Zydus Lifesciences Ltd. has been adequately tested in toxicology studies, with two acute dose toxicity studies in mice and rats by intramuscular route & intradermal route and two repeat-dose studies in rats and rabbits by intramuscular route & intradermal route. No unexpected toxicity and safety concerns were identified in these non-clinical studies during in-life Phase and terminal Phase including histopathological evaluation.

7. DESCRIPTION:

VaxiRab N contains highly concentrated, inactivated rabies virus that has been cultivated in primary chick embryo fibroblast cell cultures (PCEC). VaxiRab N produces high titers of neutralizing antibodies against rabies virus whether given before or after exposure.

The antigenic potency of VaxiRab N is determined after inactivation of the virus with β-propiolactone, using the NIH mouse protection test as recommended by the World Health Organization (WHO Technical Report Series No. 941, 2007).

8. PHARMACEUTICAL PARTICULARS.

8.1 List of excipients:

Excipients: Gelatin, Human Albumin, Sucrose.

8.2 Incompatibilities:

This product must not be mixed with other medicinal products.

8.3 Shelf Life:

The expiry date of the vaccine is indicated on the label and carton of the product.

8.4 Packaging Information:

VaxiRab N is Supplied as:

- 1 ml vial plus diluent (1 ml)
- 1 ml vial#
- 50 x 1 ml vial#

#Diluent (1 ml) provided separately

8.5 Storage:

STORE AT 2°C to 8°C (36°F to 46°F)
DO NOT FREEZE AFTER RECONSTITUTION.
PROTECT FROM LIGHT.

KEEP OUT OF REACH OF CHILDREN.

Every packing shows an expiry date of VaxiRab N and Diluent; the product should not be used after expiry date. For IM injection use immediately after reconstitution and for ID injection store at 2-8°C after reconstitution.

Reconstituted vaccine can be used up to 6 hours, provided it is stored at 2-8°C.

8.6 Special precautions for Storage:

VaxiRab N does not contain preservative; therefore, great care must be taken to avoid contamination of reconstituted vaccine. Vaccine may be used up to 6 hours after reconstitution provided it is maintained at 2 - 8° C.

Unused vaccine must be discarded after 6 hours. Using aseptic technique, a dose of vaccine may be withdrawn from a vial and the remainder used for another patient provided that the vial is stored in a refrigerator between 2 - 8° C. A new sterile needle and syringe must be used to withdraw and administer each dose of vaccine for each patient to avoid cross infection.

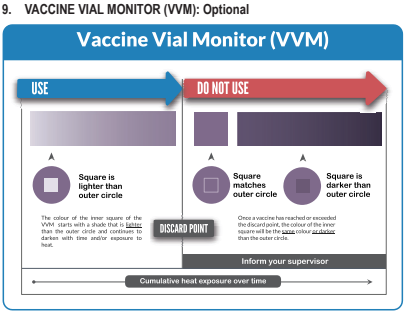
8.7 Nature and Contents of Containers:

Vaccine is filled in flint tubular USP-I glass vial fitted with Bromobutyl Rubber stopper and sealed with aluminium flip off seal.

8.8 Special precautions for disposal and other handling

Used containers shall be disposed off either as per bio-medical waste disposal instructions of respective country or through autoclaving / incineration.

9. VACCINE VIAL MONITOR (VVM): Optional



Vaccine Vial Monitor (VVM) is time-temperature sensitive dot labels that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

zydus

10. MANUFACTURED BY:

Zydus Lifesciences Limited
Survey No. 417, 419 and 420, Sarkhej Bavla N.H. No. 8 A,
Village: Moraiya, Tal.: Sanand, Dist.: Ahmedabad-382 210, India.

R5327

11. DATE OF REVISION: 09/2024

For the use of a Registered Medical Practitioner only

Rabies Vaccine BP

(Purified Chick Embryo Cell Culture Rabies Vaccine) [PCECV^{PM}]

VaxiRab N

1. GENERIC NAME: Rabies Vaccine (For Human Use)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lyophilized vial contains:
Inactivated rabies virus (Pitman Moore Strain)
Potency ≥ 2.5 IU
Virus is propagated in chick embryo fibroblast cell culture and
Inactivated by β-propiolactone
Diluent: 1ml Sterilised water for Injections B.P.

For a full list of excipients, see Section 8.1.

3. DOSAGE FORM AND STRENGTH

Dosage form: Lyophilized vaccine to be reconstituted with accompanying Sterilised water for Injections B.P. for Intramuscular or Intradermal injection.
Strength: Inactivated rabies virus (Pitman Moore Strain), Potency ≥ 2.5 IU

4. CLINICAL PARTICULARS

4.1 Therapeutic indication:

Active immunization against rabies.

(a) Pre-exposure prophylaxis (preventative, prior to exposure): Immunisation prior to possible infection with rabies, particularly for vets, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel in rabies research laboratories etc., or prior to visits to areas in which rabies is endemic (rabies infected areas).

(b) Post-exposure prophylaxis (after exposure): Treatment after contact with animals which are rabid or suspected to be rabid, or after contact with an inoculated rabies carcass.

4.2 Posology and method of administration:

Add the diluent (1ml Sterilized water for Injections BP) to the Lyophilized vaccine. The vaccine should be visually inspected both before and after reconstitution for any foreign particulate matter and / or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place. A clear solution results after reconstitution of the freeze-dried powder with the clear and colorless diluent.

For adults and children aged ≥ 2 years, the vaccine should be administered in the deltoid area of the arm; for children aged < 2 years, the anterolateral area of the thigh is recommended. Rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable.

(A) Pre-exposure vaccination:

Pre-exposure vaccination is indicated for persons at high risk of exposure (laboratory personnel, veterinarians, abattoir workers, police engaged in tasks in endemic area, animal dealers, animal handlers, workers in quarantine stations, zoologists and, in endemic areas, gamekeepers, hunters, forest rangers, forestry workers etc.). Pre-exposure vaccination is also recommended for persons (including children) who stay for an extended period (several months) in endemic areas and thus come into frequent contact with potentially rabid animals (dogs, cats, foxes, bats or other animal species at risk of rabies).

Intramuscular Route:

Pre-exposure basic immunization consists of a series of three intramuscular injections of full one dose (1 ml) on days 0, 7 and 28 (or 21), given into the deltoid muscle, or in small children, in the anterolateral thigh but never in the gluteal region.

Seroconversion is checked 2-3 weeks after the last dose. Seroconversion must be routinely checked for persons with suspected immunosuppression (through medication or disease) and in persons with a high occupational risk of exposure. The titer of neutralizing antibodies should be checked every 6 months in persons at high occupational risk; in all other persons at continued risk, the titer should be determined every year. If the titer is inadequate (≤ 0.5 IU/ml), further booster doses are given until vaccination is successful.

(B) Post - exposure measures in incomplete or unvaccinated persons:

VaxiRab N must always be used as per recommendations of the World Health Organization (WHO), depending on the type of contact with a suspected rabid animal as mentioned in below table.

Category	Type of contact	Recommended treatment
I	Touching or feeding animals, licks on the intact skin.	No treatment is required.
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding.	Immediate vaccination.
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks,licks on broken skin, exposure to bats.	Immediate vaccination and administration of immunoglobulin.

(1) Treatment of the wound: As first aid, the wound should be thoroughly cleansed with soap and water or with a detergent. A tetanus booster and antibiotic treatment may be indicated in some cases.

(2) Active vaccination with VaxiRab N

Intramuscular Route:

A series of 5 Intramuscular injections of 1 ml dose on days 0, 3, 7, 14 and 28 into the deltoid muscle, or in small children, in the anterolateral thigh, but never in the gluteal region (WHO Technical Report series 2007, No 941).
The success of vaccination (≥ 0.5 IU/ml) in immunocompromised persons at high risk should be checked by measuring the titer on day 14. Patients with a

titer that is less than 0.5 IU/ml should be given another two doses of vaccine simultaneously and as soon as possible. Further checks on the antibody titer should be made and further doses of vaccine should be administered as necessary.

Intradermal Route:

This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post-exposure regimens in countries where relevant national authorities have approved the intradermal route for rabies Post-exposure treatment.

One intradermal dose comprises 0.1 ml of reconstituted vaccine.

For VaxiRab N the administration schedule recommended in both nonimmunized and fully immunized individuals is; the 2-site Intradermal WHO endorsed regimen (known as Updated Thai Red Cross intradermal regimen, "2-2-2-0-2" regimen) that prescribes 1 injection of 0.1 ml at 2 sites on day 0, 3, 7 and 28. Two different lymphatic drainage sites, usually the left and right upper arms are selected. Updated Thai Red Cross intradermal regimen is endorsed by WHO.

It is essential that intradermal administration of VaxiRab N be carried out only by medical staff trained in this technique in order to ensure that the vaccine is delivered intradermally and not subcutaneously. For the intradermal route a sterile syringe with fixed needle (insulin type) is preferred. Correct intradermal injection should result in a raised papule with an "orange peel" appearance.

If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby. In the event that a dose of vaccine is inadvertently given subcutaneously or intramuscularly, a new dose should be administered intradermally.

The recommended dosage regimen for intramuscular or intradermal administration is summarized in below table:

Route	Dose	Number of doses	Schedule
Intramuscular	1 ml	5	Day 0, 3, 7, 14 and 28
Intradermal	0.1 ml + 0.1 ml	4	Day 0, 3, 7 and 28

The intradermal route must not be used in the following instances:

- Individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine,
- Immunocompromised individuals,
- Individuals, particularly children, with severe wounds, especially to the headand neck or presenting late for consultation.

(3) Passive Immunization with Human Rabies immunoglobulin

After a possible contamination with rabies virus through single or multiple bites or scratches, or as a result of contact of mucous membranes with saliva, post-exposure prophylaxis should be initiated with a dose of 20 IU/kg of Human rabies immunoglobulin. It is recommended that where practicable, as much of the dose as possible is infiltrated around the wound and the rest injected intramuscularly (into the gluteal region). A first dose of the rabies vaccine VaxiRab N is given at the same time. If human immunoglobulin is not available, antirabies serum of equine origin must be given in a dose of 40 IU/kg and infiltrated around the wound if possible. Before administering such a heterologous serum, an intradermal test injection must be given to check tolerability.

If rabies immunoglobulin is not available at the time of the first vaccination, it must be administered no later than 7 days after the first vaccination since later administration would result in interference with immune response of the vaccine.

Rabies immunoglobulin is not necessary if the skin remains intact, scratches or grazes are small and have not drawn blood.

Note: If dogs or cats suspected of having rabies remain healthy after an observation period of 10 days, or tissue tests show that the animal was not rabid, the active immunization can be stopped.

(C) Post-exposure immunization in previously vaccinated persons

Persons who have already received a complete series of pre- or postexposure vaccinations with VaxiRab N or in whom an antibody titer of at least 0.5 IU/ml has been previously documented, are given only two intramuscular doses of VaxiRab N, one on day 0 and the other on day 3 and do not require any rabies immunoglobulin.

Wounds should be thoroughly cleaned with soap and water or detergent.

In some cases, a tetanus booster and antibiotic treatment are indicated.

Persons previously vaccinated with a vaccine of unknown potency and in whom no documented neutralizing antibody titer of at least 0.5 IU/ml can be demonstrated, should receive a complete course of post-exposure vaccination including rabies Immunoglobulin.

4.3 Contraindications:

(a) Pre-exposure prophylaxis

In case of fever or an acute illness, vaccination should be postponed. In case of previous severe reaction to any components of the vaccine, VaxiRab N is contraindicated.

(b) Post-exposure prophylaxis

Because of the life-threatening risk of rabies, there are no contraindications to the administration of post-exposure prophylaxis using VaxiRab N. The Intradermal route must not be used in the individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine for malaria treatment or prophylaxis and in immunocompromised individuals. Such individuals may have a reduced response to intradermal rabies vaccination and should instead receive the vaccine intramuscularly.

The vaccine may contain traces of Neomycin, Amphotericin B and Gentamycin. History of anaphylactic or anaphylactoid reactions to these antibiotics are absolute contraindications.

4.4 Special warnings and precautions for use:

Immunoglobulins and rabies vaccine should not be combined in the same syringe or injected at the same site.

The possibility of allergic reactions in individuals sensitive to components of the product should be evaluated. As with all vaccines, appropriate medical treatment should be immediately available for use in the rare event of an anaphylactic reaction to the vaccine. If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g. adrenaline) and provide supportive care as required.

It is advisable to use rabies vaccines derived from non-avian sources for persons with known sensitivity to avian proteins. If such vaccines are not available, all necessary preparations should be made to treat complications which might arise in the event of an anaphylactic reaction.

Special care should be taken to ensure that the product is not injected into a blood vessel. If the vaccine is inadvertently administered into a blood vessel there is a risk of severe adverse reactions, including shock.

A separate sterile needle and syringe must be used for each individual patient to prevent the transmission of infectious agents.

As with all preparations given intramuscularly, bleeding complications may be encountered in patients with bleeding disorders

4.5 Interactions:

VaxiRab N can be given concurrently with other vaccines (particularly tetanus toxoid). No intervals need to be observed between other vaccinations. Different injectable inactivated vaccines should be administered into separate injection sites.

It is essential to check the antibody titer when vaccination is undertaken during treatment with immunosuppressants, and if necessary, to continue post-exposure immunization until the appearance of a protective antirabies antibody titer (≥ 0.5 IU/ml).

Administration of rabies immunoglobulin may be necessary for management but may attenuate the effects of concomitantly administered rabies vaccine. Therefore, it is important that rabies immunoglobulin should be administered once only for treating each at-risk exposure and with adherence to the recommended dose.

Concomitant ingestion of chloroquine for malaria prophylaxis can reduce the antibody formation after intradermal administration of rabies vaccine.

Therefore, the pre-exposure vaccination with VaxiRab N should be given by intramuscular route in persons using chloroquine in a concomitant manner.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients, etc.):

Pregnancy category C: Controlled studies in neither animals nor pregnant women are available. In life-threatening Indications, VaxiRab N can be administered because the potential benefits outweigh the possible risks.

Lactation: Administration of VaxiRab N during breast-feeding has no negative effects on the child.

Paediatric use: Paediatric individuals should receive the same dose as adults.

Geriatric use: Geriatric individuals should receive the same dose as adults.

4.7 Effects on ability to drive and use machines:

Effect of VaxiRab N on ability to drive and use machines is not known.

4.8 Undesirable Effects:

Mild reactions at the injection site, such as pain, redness, swelling or induration are possible.

More marked local reactions, fever, headache, myalgia, lymph node swelling, fatigue, arthritis, and gastrointestinal disorders may occasionally occur. Reactions such as circulatory reactions, sweating, chills, paresthesia and allergic reactions may occur rarely.

Despite the high degree of purity of the vaccine, there is a theoretical risk of inducing anaphylactic reactions in persons sensitized to avian proteins.

Rabies vaccine may cause Erythema Multiforme.

There have been isolated reports of inflammatory and demyelinating neurological disorders, such as progressive ascending paralysis (Guillain-Barré syndrome) or optic neuritis in individual cases. On the basis of currently available data, the possibility cannot be completely excluded that in rare cases immunization may induce an acute episode in patients with an autoimmune disorder (such as multiple sclerosis) or with genetic predisposition. However, there is no evidence of an increased frequency of autoimmune disorders after immunization.

4.9 Overdose:

No experience is available on the consequences of over dosage.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Mechanism of Action:

The Inactivated virus contained in VaxiRab N vaccine undergo phagocytosis by macrophages and is then transported with them into the reticuloendothelial tissue, where they stimulate the immune system to produce virus- neutralizing anti-rabies antibodies.

5.2 Pharmacodynamic properties:

VaxiRab N has been evaluated in total of 5 pre-licensure studies (1 Phase I, 2 Phase II and 2 Phase III studies). In the various pre-licensure clinical studies of VaxiRab N, all subjects who were considered for immunogenicity at various time points post-vaccination (day 14, day 28, day 90 or day 180) had an antibody titer above the seroprotective cut-off titer recommended by the WHO (0.5 IU/ml) which suggests that the vaccine generates a sufficient immune response for protection against the disease. The GMTs of antibodies at various time points were 6.4 to 26.4 fold higher than the WHO recommended seroprotective cut-off titer. Further, the antibody titers were also maintained above the WHO recommended seroprotective cut-off titer till 6 months (180 days) as assessed in one phase III clinical study.

With respect to the safety, all the adverse events reported in these studies were mild or moderate in intensity and resolved completely during the course of the study. There was also no serious adverse event reported in any of the studies.

5.3 Pharmacokinetic properties:

Not applicable.

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology

Rabies Vaccine, (Purified Chick Embryo Cell Culture Rabies Vaccine)